All I Need Is The Air That I Breathe:

A Case Study of Immunotherapy and Severe Pneumonitis

Presenter Disclosure

- **Faculty/Speaker:** Dr. Brett Finney BSc MD CCFP

- **Relationships with financial sponsors:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees:** None
  - **Other:** None

Mitigating Potential Bias

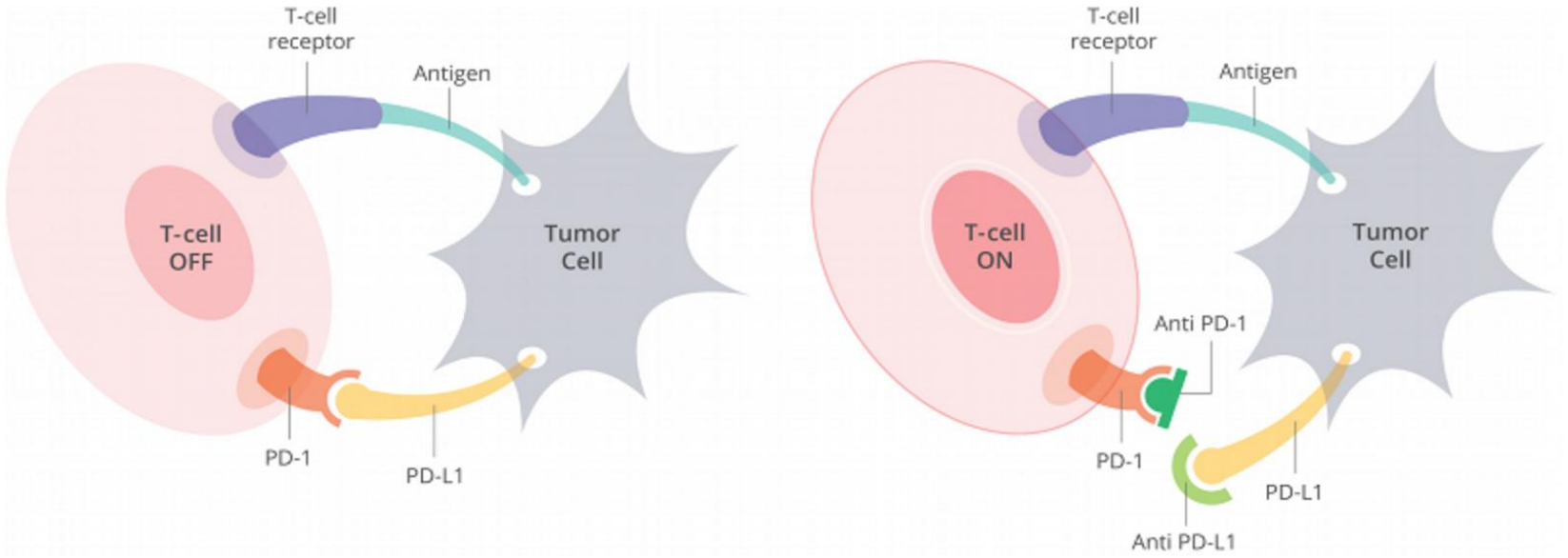
- Not Applicable

Learning Objectives

- Describe the incidence of respiratory complications as adverse events of immunotherapy
- Identify the common ways in which pneumonitis related to immunotherapy can present
- Explain the differential diagnosis and work up of suspected respiratory complications related to immunotherapy

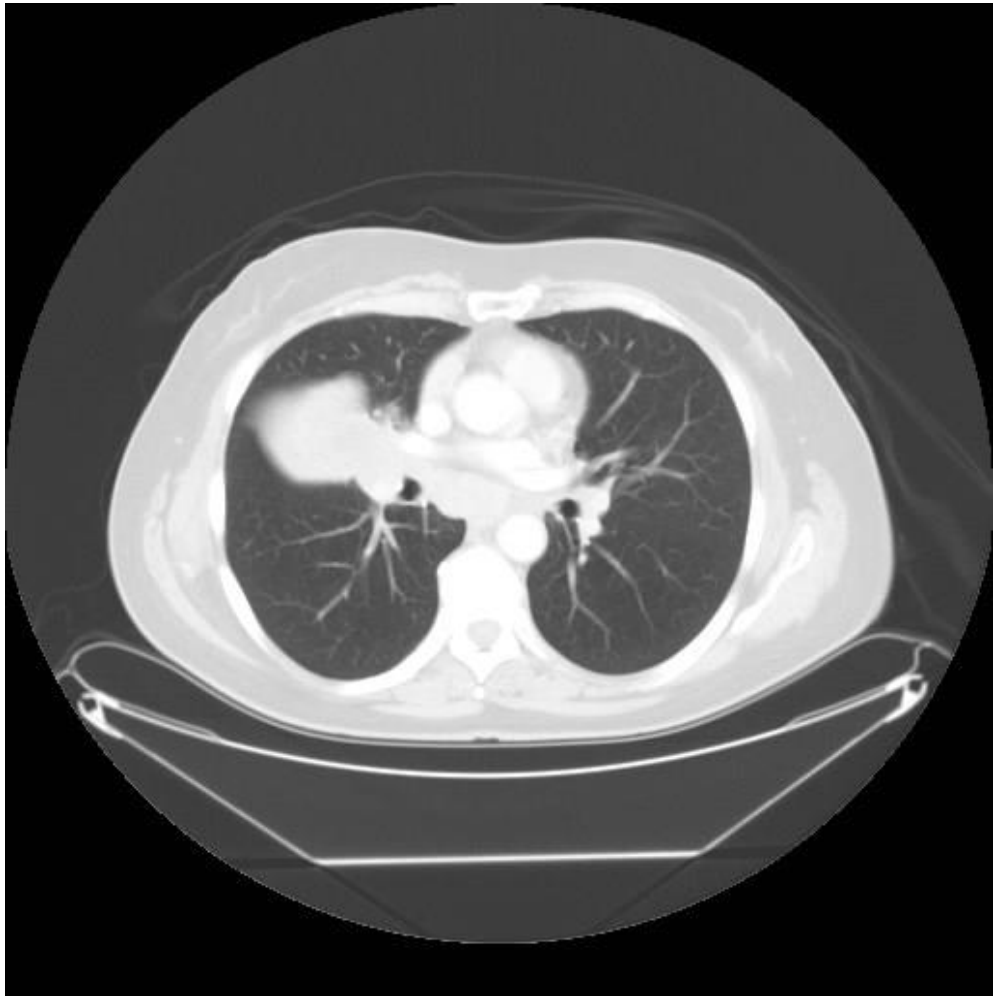
Immune Checkpoint Inhibitors

- Anti-CTLA4 (ipilimumab)
- PD-1 (pembrolizumab, nivolumab)
- PD-L1 (durvalumab)

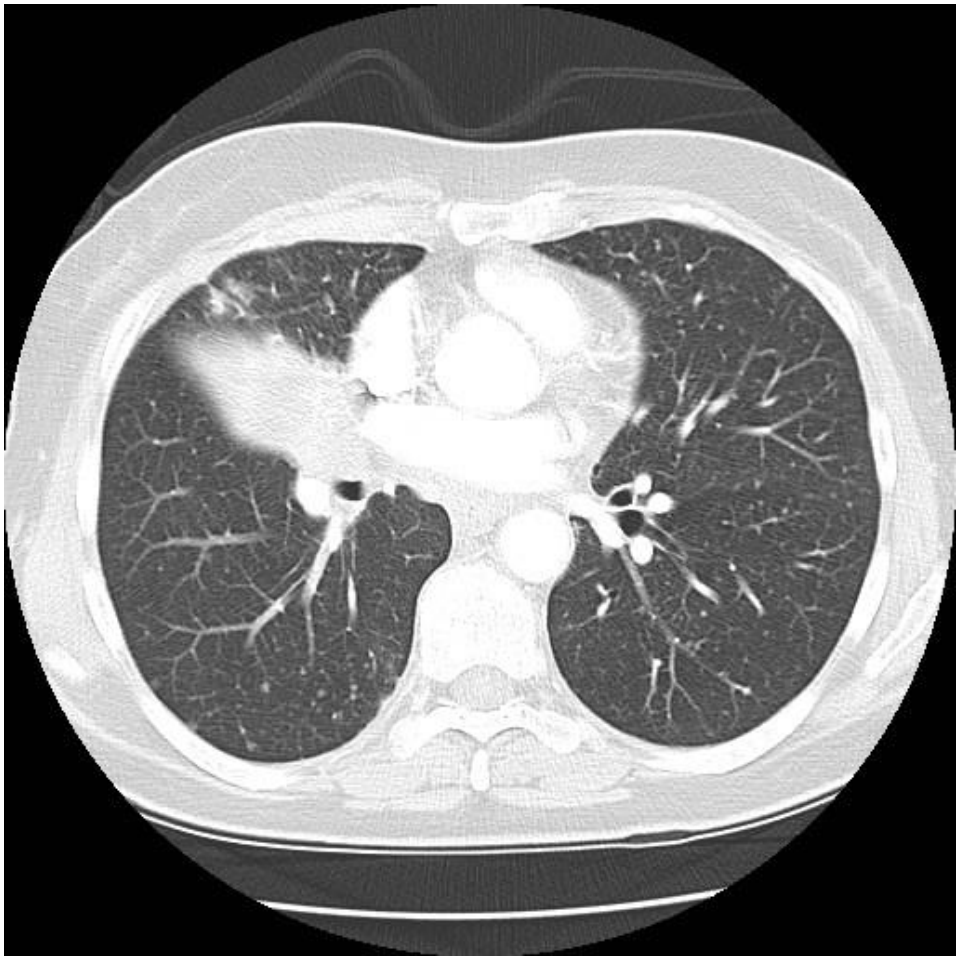


- 66 year old diagnosed with T3 N3 M0 Stage IIIB adenocarcinoma of the right lung
- 25 pack year smoker (quit shortly after diagnosis)
- ECOG 0 at time of diagnosis, mild shortness of breath
- No complicating medical conditions

CT at diagnosis



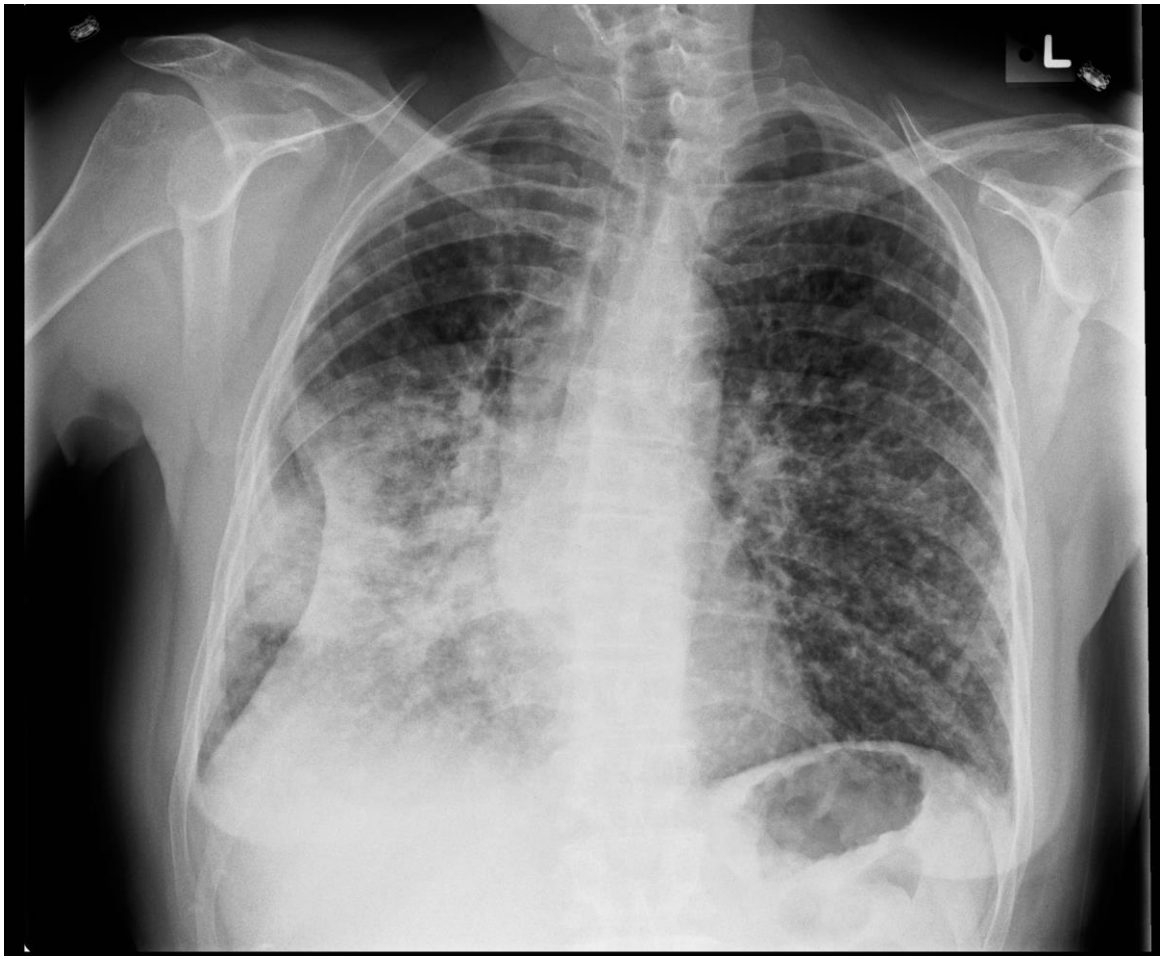
CT image from pre Nivolumab



Day 12

- Cycle 1, Day 12 presents to ER with non productive cough, chest pain with deep breaths, and increasing shortness of breath, progressive since onset Day 7
- BP 94/61 HR 134 RR 24 Temp 36.6 SpO2 88% RA GCS 15
- Chemistry normal, WBC 12 Hgb 125 Plt 376

Day 12 CXR images



Differential Diagnosis

- Pneumonia
- Pulmonary embolism
- Progression of malignancy
- Pneumonitis secondary to immunotherapy (irAE)
- Opportunistic infections (ie pneumocystis)

irAE: Pneumonitis

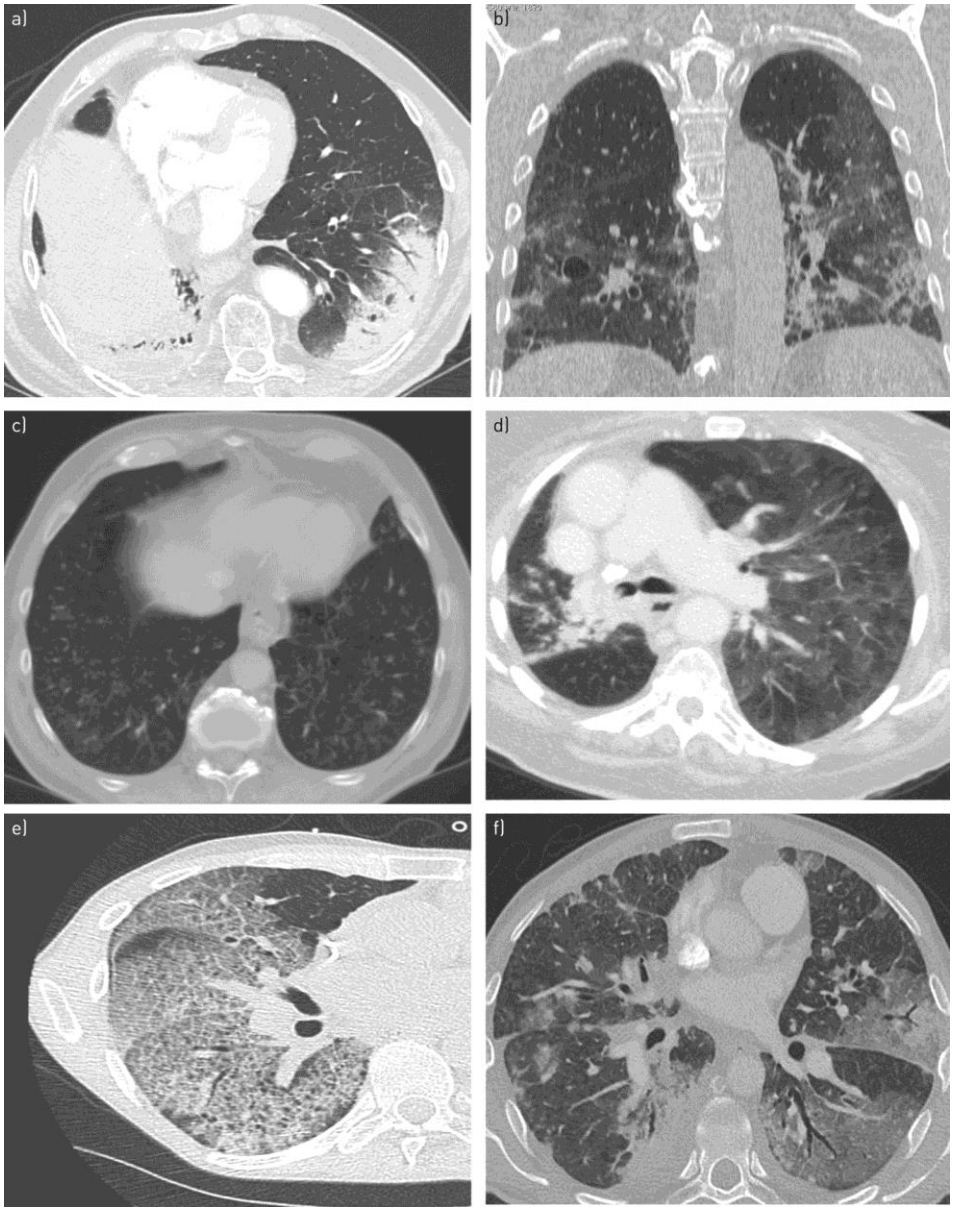
- Pneumonitis occurs in about 3% of patients
- Dyspnea 53%
- Cough 35%
- Fever 12%
- Chest pain 7%
- Grade 1-2 72%
- To date, immune-induced pneumonitis remains relatively poorly described

Haanen et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up, Annals of Oncology 28 (Supp 4): iv119-iv142, 2017

Pneumonitis

- Time of onset: 9 days to 19.2 months, median 2.8 months
- Incidence is similar in patients with melanoma vs NSCLC
- 72% Grade 1-2, 86% improved with drug withholding or immunosuppression
- Grade 3-4 events of 1-2%, fatal pneumonitis at 0.2%, and discontinuation due to pneumonitis in 0.2-4%
- Acute interstitial pneumonitis/diffuse alveolar damage syndrome (DADS), organizing inflammatory pneumonia, and sarcoidosis-like pulmonary granulomatosis

- Haanen et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up, Annals of Oncology 28 (Supp 4): iv119-iv142, 2017

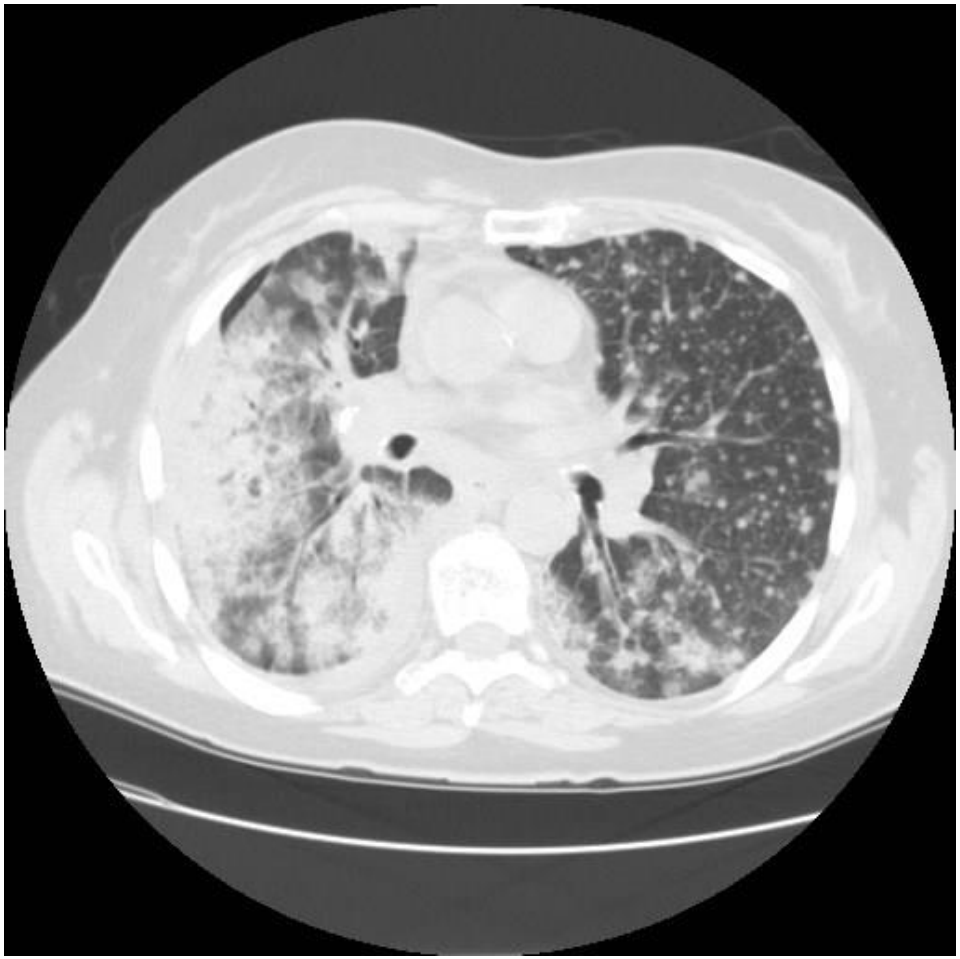


Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients
Myriam Delaunay, Jacques Cadranel,et. al, European Respiratory Journal Aug 2017, 50 (2) 1700050; **DOI:** 10.1183/13993003.00050-2017

Day 13

- Day 13 described as stable with slight improvement
- BP 102/58 HR 114 RR 22 SpO2 92% on 4 L NP, Temp 37.8
- “Decreased air entry to RLL with creps”
- WBC 12.2 Hgb 123 Plt 361, normal chemistry
- CT – No PE, multiple mediastinal and hilar lymph nodes, new small right pleural effusion, extensive pulmonary nodules through the hemithoraces, confluent areas of airspace opacity with the right lower lobe

Who you gonna call?



- Day 13, 22:30, “Feeling worse, restless, increased shortness of breath, fever”
- BP 83/55 HR 157 RR 40 SpO2 81% on 4L NP Temp 38.4
- “Poor air entry to right lower lobe”
- WBC 12.2 Chemistry unchanged
- Venous gas: pH 7.42 pCO2 32 HCO3 21 Lactate 1.03
- Initial management IV crystalloid bolus, IV Piperacillin/tazobactam and vancomycin, oxygen titration

Day 14

- BP 103/60 HR 124 RR 36 SpO2 95% 6L FM Temp 38.3 Venous gas: pH 7.47 pCO2 33 HCO3 24 Lactate 1.25
- Azithromycin added to antibiotic regimen and started IV methylprednisolone 100 mg q24 hours
- 12:56: “Deteriorating, decreased air entry to bilateral lower lobes with fine creps throughout inspiration”
- BP 115/70 HR 120 RR 40 SpO2 87 % on 9 L NR FM Temp 37.2

- Transferred to ICU, BiPap initiated
- Patient has normal mentation, able to eat with mask off for brief periods, but quickly became dyspneic
- WBC 16 Hgb 115 Plt 359 Normal chemistry
- Venous gas: pH 7.39 pCO2 38 HCO3 23 lactate 1.89
- Discussed with medical oncologist
- Plan to consider short term intubation and bronchoscopy if further deterioration to perform BAL

- Bipap discontinued after 8 hours, about 12 hours after IV steroids initiated
- Day 16 - SpO2 low 90's on 5L facemask, HR 66
- Blood cultures negative
- Day 19 – On medical ward, 3L/min by NP, Afebrile, improved breath sounds, all cultures remained negative. Changed to oral prednisone with a 10 week tapering course planned

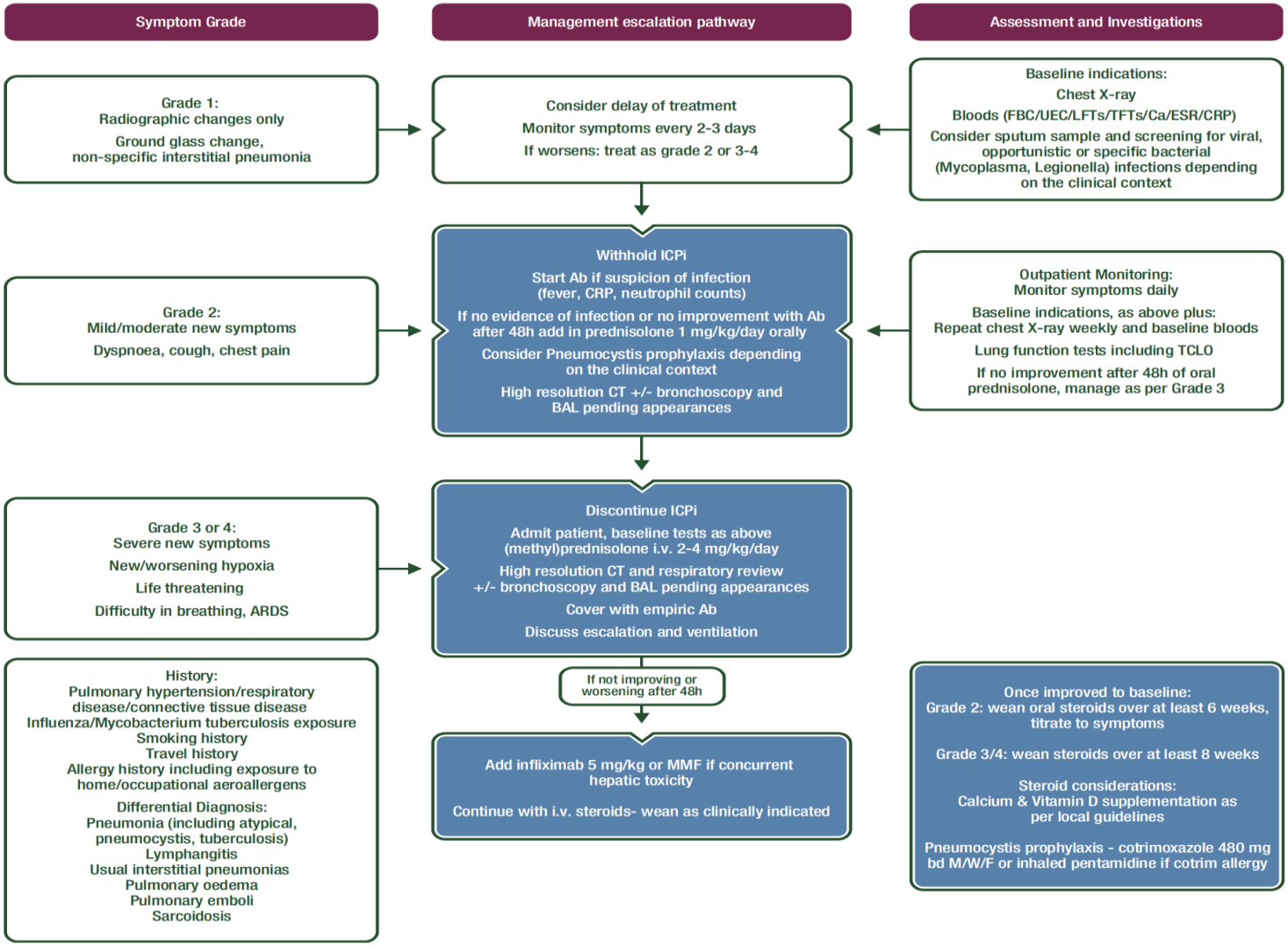


Figure 9. ICPi-related toxicity: management of pneumonitis.
Ab, antibody; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; bd M/W/F, twice daily Monday/Wednesday/Friday; Ca, calcium; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; FBC, full blood count; ICPi, immune checkpoint inhibitor; i.v., intravenous; LFT, liver function tests; MMF, mycophenolate mofetil; TCLO, transfer factor for carbon monoxide; TFT, thyroid function tests; UEC, urea, electrolytes, creatinine.

Haanen et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up, Annals of Oncology 28 (Supp 4): iv119-iv142, 2017

Resources

- Haanen et al. **Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up**, Annals of Oncology 28 (Supp 4): iv119-iv142, 2017
- Brahmer et al. **Management of Immune Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline**, Journal of Clinical Oncology Vol 36 Number 17, 1714-1768, 2018